General

Guideline Title

Measuring fractional exhaled nitric oxide concentration in asthma: NIOX MINO, NIOX VERO and NObreath.

Bibliographic Source(s)

National Institute for Health and Care Excellence (NICE). Measuring fractional exhaled nitric oxide concentration in asthma: NIOX MINO, NIOX VERO and NObreath. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Apr. 52 p. (Diagnostics guidance; no. 12).

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Fractional exhaled nitric oxide (FeNO) testing is recommended as an option to help diagnose asthma in adults and children:

- Who, after initial clinical examination, are considered to have an intermediate probability of having asthma (as defined in the Scottish Intercollegiate Guidelines Network/British Thoracic Society [SIGN/BTS] guideline *British guideline on the management of asthma. A national clinical guideline*) and
- When FeNO testing is intended to be done in combination with other diagnostic options according to the British guideline on the management of asthma (2012).
  Further investigation is recommended for people whose FeNO test result is negative because a negative result does not exclude asthma.

FeNO measurement is recommended as an option to support asthma management (in conjunction with the SIGN/BTS guideline *British guideline on the management of asthma. A national clinical guideline*) in people who are symptomatic despite using inhaled corticosteroids.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Asthma

Guideline Category

Diagnosis

Evaluation

Management

Technology Assessment

Clinical Specialty

Allergy and Immunology

Family Practice

Geriatrics

Internal Medicine

Pediatrics

Pulmonary Medicine

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Respiratory Care Practitioners

Guideline Objective(s)

To evaluate the clinical and cost effectiveness of measuring fractional exhaled nitric oxide (FeNO) concentration (using NIOX MINO, NIOX VERO and NObreath) in the diagnosis and management of asthma

Target Population

People with clinical characteristics suggestive of asthma, including:

- Any patient 5 years old or older presenting to primary care with symptoms of asthma
- People with clinical characteristics suggestive of asthma who are difficult to diagnose
- Patients who may experience different outcomes from the use of fractional exhaled nitric oxide (FeNO) when compared to the main population under assessment defined as smokers, the elderly and pregnant women

Interventions and Practices Considered

NIOX MINO, NIOX VERO and NObreath devices

Major Outcomes Considered

- Diagnostic accuracy of fractional exhaled nitric oxide (FeNO) tests
- Test failure rate
- Asthma control
- Exacerbation rates
- Clinical complications associated with acute exacerbations
- Levels of inhaled corticosteroids
- Use of oral corticosteroids
- Adverse effects of treatments
- Health-related quality of life (HRQoL)
- Mortality
- Cost-effectiveness

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Care Excellence (NICE) commissioned an External Assessment Group to perform a systematic literature review on the technology considered in this diagnostics guidance and prepare a Diagnostics Assessment Report (DAR). The DAR for this guidance was prepared by the School of Health and Related Research (ScHARR), University of Sheffield (see the "Availability of Companion Documents" field).

Clinical Review

Methods

Two systematic reviews and one rapid review were conducted concurrently to identify clinical evidence relevant to the decision problem.

1. Rapid review of equivalence of fractional exhaled nitric oxide (FeNO) devices
2. Systematic review of diagnostic accuracy of FeNO for asthma
3. Systematic review of the efficacy of FeNO-guided management of asthma

Clinical Reviews Search Methodology

Systematic searches were carried out between March 2013 and April 2013. For the review of device equivalence, and for both diagnostic and management reviews, the following databases were searched:

- MEDLINE and MEDLINE In Process: Ovid. 1948-present
- EMBASE: Ovid. 1974-present
- Cochrane Library
    - Cochrane Database of Systematic Reviews (CDSR) 1996-present
    - Database of Abstracts of Reviews of Effects (DARE) 1995-present
    - Cochrane Central Register of Controlled Trials (CCRCT) 1998-present
    - Health Technology Assessment Database (HTA) 1995-present
    - National Health Service Economic Evaluation Database (NHS EED) 1995-present
- Science Citation Index Expanded (SCIE): Web of Science 1999-present
- Conference Proceedings Citation Index – Science (CPCI-S): Web of Science. 1990-present

The following trial registers and websites were searched in March 2013 for all three reviews (search terms used are provided in Appendix 2 in the DAR):

- ClinicalTrials.gov http://clinicaltrials.gov/
- metaRegister of Controlled Trials http://www.controlled-trials.com/mrct/
- U.S. Food and Drug Administration (FDA) Manufacturer and User Facility Device (MAUDE) http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/search.cfm
- EuroScan International Network http://euroscan.org.uk/

Management Review Searches

Searches for the management review were developed following the identification of a 2009 Cochrane review. Study design filters were not applied to the strategy in case lower levels of evidence were needed for the subgroups defined *a priori* in the protocol. The strategy is made up of free-text terms for NIOX MINO and NObreath including manufacturer names, subject headings and free-text terms for asthma (e.g., respiratory hypersensitivity, bronchoconstriction) and lower respiratory tract symptoms (e.g., coughing, wheezing, chest pain) that were combined with terms for exhaled nitric oxide (e.g., feno, eno). Searches were limited to publications since 2009.

A summary of the search records retrieved from the searches is provided in Table 6 in the DAR.

Diagnostic Review Searches

Similar to the management review search strategy, the diagnostic search comprises terms for NIOX MINO and NObreath including manufacturer names, subject heading and free-text terms for asthma and lower respiratory tract symptoms combined with terms for exhaled nitric oxide. The strategy was combined with three filters 1) systematic reviews filter 2) a randomised controlled trial (RCT) filter 3) a diagnostic filter. No date limits were applied to the searches.

A summary of the search records retrieved from the searches is given in Table 7 in the DAR.

Equivalence of Devices Review Searches

The analytic validity studies search for NIOX MINO and NObreath was carried out using terms for NIOX MINO, NObreath and the manufacturer names without any application of filters and limits in the database listed. The number of records retrieved is included in Table 7 in the DAR (final column).

Additional Search for NIOX VERO

Aerocrine's new device, NIOX VERO, will be launched shortly and was brought to the attention of the ERG in July 2013. An additional search was conducted on 13th August 2013 to check for any publications relating to this device that would have been missed by the original search. This search comprised simply the term "Niox Vero" across all previously listed databases. A summary of the search records retrieved from the searches is given in Table 8 in the DAR.

Reference Management

All retrieved citations were downloaded into Reference Manager® bibliographic software and deduplicated to include only unique citations.

Study Selection

Retrieved citations were considered for inclusion in several stages. Firstly, titles were considered and any studies obviously not relevant were excluded. Secondly, abstracts were consulted. At this stage, tags were applied to studies in Reference Manager® to identify the device used, the age group of the participants and the study design. In instances whereby it was obvious which review the study was likely to inform, this tag was also applied. In the third stage, articles tagged as the highest levels of evidence for each review were retrieved and the full text was obtained for comparison against the inclusion and exclusion criteria.

Once the full text selection process was complete, a decision was made as to whether there were gaps in the evidence that would require lower levels of evidence to be consulted. This was the case for the diagnostic review, where no end-to-end studies were identified; for the management review, where only limited evidence was identified using NIOX MINO and no evidence was identified relating to NObreath; and for some of the subgroups of interest to the review. For the diagnostic review, studies including any device were included rather than just those using NIOX MINO, NIOX VERO or NObreath; for the management review studies using any FeNO device were included; and the rapid review of the equivalence of devices was conducted in full. Refer to the DAR for the information on search terms used to retrieve relevant titles for the subgroups of interest to the review.

Refer to Tables 9, 10, and 11 in the DAR for the inclusion and exclusion criteria used for the review of equivalence of devices, review of diagnostic accuracy, and review of FeNO guided management of asthma, respectively.

The Cost-effectiveness of FeNO Testing for the Diagnosis and Management of Asthma

Review of Existing Evidence Relating to the Cost-effectiveness of FeNO Testing for the Diagnosis and Management of Asthma

Review Methods

Methods Used to Identify Existing Economic Studies

Systematic searches across a range of electronic databases were undertaken to identify published studies of FeNO testing for the diagnosis and/or management of asthma. Other economic studies of interventions for the diagnosis or management of asthma were also searched. All searches were undertaken by an Information Specialist during the period 30th May 2013 to 7th June 2013.

Four separate strands of searching were undertaken; these are detailed below.

Economic Search 1: NIOX MINO/NObreath in Either the Diagnosis or Management of Asthma (30th May 2013)

This search used free-text terms relating to NIOX MINO and NObreath (including manufacturer names); these terms were combined with a sensitive economic search filter.

Economic Search 2: Models of Asthma and FeNO (30th May 2013)

This search used the search strategies developed for the management studies in the clinical effectiveness review (see above) and combined these with a sensitive economic search filter. Studies that were found in the first search would also be retrieved in this search.

Economic Search 3: Asthma Management Models (3rd June 2013)

This focussed search used free-text terms for asthma combined with cost terms in the title and the economic model subject heading. A sensitive economic filter was not applied in this search.

Economic Search 4: Asthma Diagnostic Models (7th June 2013)

This focussed search used free-text terms for asthma (as used in the asthma management model search [economic search 3 described above]) combined with a sensitive economic evaluations search filter and a diagnostic search filter.

These four searches are shown diagrammatically in Figure 20 in the DAR.

All of the above searches were performed within the following databases:

- MEDLINE and MEDLINE In Process: Ovid. 1948-present
- EMBASE: Ovid. 1974-present
- Cochrane Library: Wiley Interscience
    - Cochrane Database of Systematic Reviews (CDSR) 1996-present
    - Health Technology Assessment Database (HTA) 1995-present
    - NHS Economic Evaluation Database (NHS EED) 1995-present
- Science Citation Index Expanded (SCIE): Web of Science 1999-present
- Conference Proceedings Citation Index – Science (CPCI-S): Web of Science. 1990-present

The economic MEDLINE search strategy is detailed in Appendix 14 in the DAR.

An additional separate search was also undertaken to identify evidence relating to NIOX VERO in August 2013.

Inclusion and Exclusion Criteria for the Review

Given the anticipated dearth of published economic analyses of studies relating to FeNO, the External Assessment Group adopted broad inclusion criteria for the review.

Inclusion Criteria

- Economic analyses of costs and consequences of interventions for the diagnosis and/or management of asthma in children and/or adults
- Studies reporting on the cost-effectiveness of NIOX MINO, NIOX VERO or NObreath for the diagnosis or management of asthma

Exclusion Criteria

- Letters, commentaries and editorials
- Economic studies which do not relate to diagnostic or management interventions
- Studies which do not relate to asthma
- Studies which do not involve (i) a model-based analysis, (ii) economic evaluations alongside trials or other forms of empirical clinical study or (iii) estimates of the costs and consequences of FeNO testing for the diagnosis of asthma

Data Sifting

The titles and abstracts of all records identified by the search were reviewed by one member of the research team. The full text of studies considered eligible for inclusion were then retrieved for a more detailed examination.

Number of Source Documents

Clinical Review

A total of 4861 citations were retrieved and considered for inclusion in the review. After scrutiny of the titles and abstract, 4436 studies were excluded and the full text of 425 citations were obtained and consulted. Of these, 347 were excluded (see Appendix 6 in the Diagnostics Assessment Report [DAR] [see the "Availability of Companion Documents" field]) and 62 studies (78 citations) were included in the review.

For the review of subgroups, a total of 162 citations were identified of which 15 studies were included. Appendix 7 in the DAR summarises the process of identifying and selecting relevant literature.

The Cost-effectiveness of FeNO Testing for the Diagnosis and Management of Asthma

A total of 1,898 potentially relevant citations were identified from the four strands of searches. The full texts of 27 studies were retrieved for further examination. The full text of one of these studies could not be retrieved and was excluded. Of the remainder, only two studies were identified which related to fractional exhaled nitric oxide (FeNO) testing in the diagnosis and/or management of asthma. The focussed searches did not identify any further cost-utility models of other interventions for the diagnosis of asthma. Sifting of the focussed management model searches identified a further thirteen studies which were used more generally to inform the model structure, although none of these relate to FeNO testing. In addition, one additional management study which was detailed in the appendices of a UK Health Technology Assessment (HTA) report was identified.

In addition, one of the manufacturers submitted evidence relating to the cost-effectiveness of NIOX MINO for the diagnosis and management of asthma. This submission is included as part of the economic review. The manufacturer did not submit any economic evidence relating to the cost-effectiveness of the NIOX VERO device. The other manufacturer did not submit any evidence relating to either the effectiveness or cost-effectiveness of the NObreath device.

Two *de novo* models were submitted by the External Assessment Group.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Meta-Analysis of Randomized Controlled Trials

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Care Excellence (NICE) commissioned an External Assessment Group to perform a systematic literature review on the technology considered in this diagnostics guidance and prepare a Diagnostics Assessment Report (DAR). The DAR for this guidance was prepared by the School of Health and Related Research (ScHARR), University of Sheffield (see the "Availability of Companion Documents" field).

Clinical Review

Methods

Data Extraction

A different standardised data extraction form was developed for each review following the guidelines given in the Centre for Reviews and Dissemination (CRD) handbook for systematic reviews and the Cochrane Handbook and piloted using two studies per review. Missing fields were added as appropriate and back-filled where necessary. Appendix 4 in the DAR lists the fields that were data extracted for each review. Data were extracted from the studies by one of three reviewers and was then checked by a second reviewer, except in the rapid review of equivalence of devices where a sole reviewer extracted all relevant data. Any discrepancies were resolved by discussion, with involvement of a third reviewer when necessary. Where appropriate, authors were contacted for missing or unclear data. Data from multiple publications of the same study were extracted and quality assessed as a single study. In a change from the protocol, data were not extracted from existing systematic reviews, but directly from the primary research journal articles and conference abstracts.

Quality Assessment

As a rapid review, quality assessment was not conducted for the review of equivalence of devices.

Diagnostic cohort studies were assessed using Quality Assessment of Diagnostic Accuracy Studies II (QUADAS II). The tool was adapted to the specifics of this appraisal and the scoring scheme can be found in Appendix 5 in the DAR.

Management randomised controlled trial (RCT) studies were assessed using domains listed in the Cochrane risk of bias tool. The scoring scheme can also be found in Appendix 5 in the DAR.

Studies of lower quality were not formally quality assessed but were considered on their individual merits.

Quality assessment was conducted by one reviewer and checked by a second. A third reviewer was consulted in cases of disagreement.

Analysis and Synthesis

A narrative synthesis was conducted for the rapid review of the equivalence of devices and no meta-analysis was planned or attempted.

A narrative synthesis was conducted for the review of diagnostic studies. A meta-analysis was planned where sufficient studies of acceptable clinical heterogeneity in terms of patient populations, devices, cut-off points and reference standards were available. A meta-regression to allow the use of multiple cut-off points in the modelling was planned, again, should the necessary data be available with appropriate levels of heterogeneity between studies. However, data were not suitable for meta-analysis or meta-regression.

A narrative synthesis was conducted for the review of management studies. A meta-analysis was planned where enough studies of acceptable clinical heterogeneity in terms of patient populations, devices, cut-off points, interventions, comparators, and outcomes were available. Clinical heterogeneity indicated that such an analysis was unlikely to produce meaningful results, but exploratory analyses and sensitivity analyses to elements of study design were conducted in the review of adults, even though clinical heterogeneity was high. For rate outcomes, the generic inverse variance method was used in Review Manager® to meta-analyse rate ratios. For continuous outcomes, a standardised mean difference analysis was conducted as metrics for inhaled corticosteroid (ICS) use were different.

In all cases, fixed effects were used first, and random effects applied if the I^2 statistic indicated that heterogeneity was moderate or high. This was judged to be the case at >40%.

Refer to Section 5 in the DAR for more information on clinical effectiveness analysis.

The Cost-effectiveness of FeNO Testing for the Diagnosis and Management of Asthma

Review of Existing Evidence Relating to the Cost-effectiveness of FeNO Testing for the Diagnosis and Management of Asthma

Review Methods

Critical Appraisal Methods

The identified studies of fractional exhaled nitric oxide (FeNO) were critically appraised using the Drummond checklist for economic evaluations and the NICE Reference Case for diagnostic studies. The identified studies were also informally assessed against current guidelines for the development and reporting of health economic models. Studies of other interventions for the diagnosis and/or management of asthma were not subjected to a formal critical appraisal but were instead used to inform the design and development of the *de novo* health economic analyses.

Development of Two *de novo* Models to Estimate the Cost-effectiveness of FeNO Testing for the Diagnosis and Management of Asthma

The External Assessment Group (EAG) analysis involves the development of two models: (1) a *de novo* model to assess the expected cost-effectiveness of FeNO testing in addition to or in place of standard tests for the diagnosis of asthma and (2) a *de novo* model to assess the expected cost-effectiveness of FeNO plus standard guidelines versus standard guidelines for the management of patients with diagnosed asthma. Whilst these models are distinct, they form part of the same overall asthma service pathway, hence they share a number of parameter values and assumptions.

The EAG Asthma Diagnostic Model

Model Structure

Figure 25 in the DAR presents the structure of the EAG diagnostic model. The model is implemented as a simple decision tree. The population under consideration may or may not have true underlying asthma. The model then uses estimates of sensitivity and specificity associated with each diagnostic test, or combination of tests, to estimate the expected probability that a patient will be diagnosed as having asthma or not having asthma. Therefore, the model estimates the probability that a patient with asthma will be correctly or incorrectly diagnosed as true-positive or false-negative respectively, and the probability that a patient without asthma will be correctly or incorrectly diagnosed as true-negative or false-positive respectively. The model makes the simplifying assumption that incorrect diagnoses (false-negatives and false-positives) are resolved by subsequent tests after some period of time. Unnecessary treatment costs and health losses resulting from misdiagnosis are explicitly captured in the model.

The diagnostic model estimates costs and health outcomes for each diagnostic option across four groups:

- Patients who are true-positive (test sensitivity x prevalence) are assumed to require the initial diagnostic test(s) with no subsequent tests and are assumed to have their asthma controlled using inhaled corticosteroids (ICS) plus long-acting beta-agonists (LABA).
- Patients who are true-negative (test specificity x [1-prevalence]) are assumed to incur the cost of the initial test(s) with no subsequent tests and are assumed to have normal (general population) health status for the remainder of the model time horizon.
- Patients who are false-positive ([1-test sensitivity] x [1-prevalence]) are assumed to incur the cost of the initial test(s) with subsequent tests to correct their initial misdiagnosis. These patients and are assumed to incur a reduction in health status and incur the costs of ICS and LABA until their misdiagnosis is corrected.
- Patients who are false-negative ([1-test sensitivity] x prevalence) are assumed to incur the cost of the initial test(s) with subsequent tests to correct their initial misdiagnosis. These patients are assumed to lose health due to poor control until their asthma is correctly diagnosed. These patients are assumed to incur asthma management costs after their asthma is diagnosed for the remainder of the model time horizon. These patients also accrue costs associated with an increased rate of exacerbations until their misdiagnosis is corrected.

The EAG Asthma Management Model

Model Structure

Figure 26 in the DAR presents the structure of the *de novo* EAG management model. The model adopts a simple Markov framework with two states: (1) alive with diagnosed asthma and (2) dead. The model assumes that differences in health-related quality of life (HRQoL) between treatment groups in the alive state are driven by the incidence of exacerbations, whilst cost differences are influenced by the exacerbation rate and the mean level of medication use in each treatment group. Each exacerbation is associated with a reduction in HRQoL and a cost of management. Exacerbations which require hospitalisation are assumed to have a greater impact on HRQoL loss and are assumed to be more expensive to treat compared to other less severe exacerbations. Within each treatment group, the rate of exacerbations is modelled together with an estimate of required medication over time.

Refer to Section 6 in the DAR for additional information on cost-effectiveness.

Methods Used to Formulate the Recommendations

Description of Methods Used to Formulate the Recommendations

Developing Recommendations

After reviewing the evidence the Diagnostic Advisory Committee (DAC) agrees draft recommendations on the use of the technology in the National Health Service (NHS) in England. When formulating these recommendations, the Committee has discretion to consider those factors it believes are most appropriate to the evaluation. In doing so, the Committee has regard to any relevant provisions of the National Institute for Health and Care Excellence's (NICE's) Directions, set out by the Secretary of State for Health, and legislation on human rights, discrimination and equality. In undertaking evaluations of healthcare technologies, NICE takes into account the broad balance of clinical benefits and costs, the degree of clinical need of patients under consideration, any guidance issued to the NHS by the Secretary of State that is specifically drawn to the attention of NICE by the Secretary of State, and any guidance issued by the Secretary of State, and the potential for long-term benefits to the NHS of innovation.

The Committee takes into account advice from NICE on the approach it should take to making scientific and social value judgements. Advice on social value judgements is informed in part by the work of NICE's Citizens Council.

The Committee takes into account how its judgements have a bearing on distributive justice or legal requirements in relation to human rights, discrimination and equality. Such characteristics include, but are not confined to: race, gender, disability, religion or belief, sexual orientation, gender reassignment and pregnancy or maternity.

The Committee considers the application of other Board-approved NICE methods policies, such as the supplementary guidance on discounting and the end-of-life criteria, if they are relevant to the evaluation.

Because the Programme often evaluates new technologies that have a thin evidence base, in formulating its recommendations the Committee balances the quality and quantity of evidence with the expected value of the technology to the NHS and the public.

The credibility of the guidance produced by NICE depends on the transparency of the DAC's decision-making process. It is crucial that the DAC's decisions are explained clearly, and that the contributions of registered stakeholders and the views of members of the public are considered. The reasoning behind the Committee's recommendations is explained, with reference to the factors that have been taken into account.

The language and style used in the documents produced by the Committee are governed by the following principles:

- Clarity is essential in explaining how the DAC has come to its conclusions.
- The text of the documents does not need to reiterate all the factual information that can be found in the information published alongside the guidance. This needs careful judgement so that enough information and justification is given in the recommendations to enable the reader to understand what evidence the DAC considered and, if appropriate, who provided that evidence.

The Committee may take into account factors that may provide benefits to the NHS or the population, such as patient convenience. It may also consider costs and other positive or negative impacts on the NHS that may not be captured in the reference-case cost analysis, such as improved processes.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

Base-Case Results

The base-case model was evaluated probabilistically using Monte Carlo sampling techniques. Deterministic one-way sensitivity analyses were also performed to account for different modelling assumptions. Central estimates of cost-effectiveness were presented as incremental cost-effectiveness ratios (ICERs). Uncertainty surrounding the cost-effectiveness estimates was presented using cost-effectiveness planes and cost-effectiveness acceptability curves.

The base-case results of the diagnostic model in children and adults suggested that, across the 17 diagnostic options included in the economic analysis, the expected difference in quality-adjusted life years (QALYs) is likely to be small (4.2686–4.2834). They also suggested that airway hyperresponsiveness (methacholine challenge test) is expected to produce the greatest QALY gain (4.2834), followed by fractional exhaled nitric oxide (FeNO) testing (either NObreath, NIOX VERO or NIOX MINO) plus bronchodilator reversibility, with a QALY of 4.2829. The difference between the QALYs produced by the methacholine challenge test and FeNO testing plus a bronchodilator was very small (0.0005 QALYs). Other diagnostic test options, either with or without FeNO testing, resulted in increasingly lower QALYS, with spirometry (forced expiratory volume in the first second divided by the total volume of air that a person can forcibly exhale in one breath) producing the lowest QALY gain of 4.2686.

The External Assessment Group presented an incremental cost-effectiveness analysis, in which the diagnostic options were ranked in decreasing order of QALY. The ICER for airway hyper-responsiveness (methacholine challenge test) compared with the next best option in terms of QALY (NObreath plus bronchodilator reversibility) was approximately £1.125 million per QALY gained. Following methacholine challenge, the option producing the next best QALY (FeNO testing plus bronchodilator reversibility) yielded 4.2829 QALYs, but the cost associated with the individual tests varied (£686.08 for NObreath, £687.61 for NIOX VERO and £688.33 for NIOX MINO). FeNO testing plus bronchodilator reversibility is therefore cost saving compared with methacholine challenge, but is estimated to produce marginally fewer QALYs (see above). All further options, with or without FeNO testing, were dominated because they were both more expensive and produced fewer QALYs. The External Assessment Group considered these results to be very uncertain.

Results in Children

The base-case results for asthma management in children suggested that the British guideline (see the Scottish Intercollegiate Guidelines Network/British Thoracic Society [SIGN/BTS] guideline *British guideline on the management of asthma. A national clinical guideline*) plus FeNO measurement produces a small health benefit (0.05 QALYs) compared with the British guideline alone. The British guideline plus FeNO measurement was also more costly (£8148.59 for the British guideline plus NObreath, £8314.30 for the British guideline plus NIOX VERO and £8391.53 for the British guideline plus NIOX MINO) than the British guideline alone (£5860.06) because of projected inhaled corticosteroid use for the FeNO measurement groups. The resulting ICER for NObreath plus the British guideline compared with the British guideline alone was £45,213 per QALY gained. NIOX VERO and NIOX MINO were expected to be dominated by NObreath because of their higher marginal per-test costs.

Results in Adults

The base-case results for asthma management in adults showed that the British guideline plus FeNO measurement is expected to produce a small health benefit (0.04 QALYs) compared with the British guideline alone. The British guideline plus FeNO measurement was also more costly in adults (£7377.61 for the British guideline plus NObreath, £7535.43 for the British guideline plus NIOX VERO and £7608.99 for the British guideline plus NIOX MINO) than the British guideline alone (£7296.30) because of increased inhaled corticosteroid use in the FeNO measurement groups during the first 12 months of monitoring. Similarly to the children's model for asthma management, the model assumed that all 3 FeNO devices produce the same health benefits. NIOX MINO and NIOX VERO were dominated by NObreath because of their higher marginal per-test costs. The ICER of the British guideline plus NObreath compared with the British guideline alone was approximately £2146 per QALY gained. If dominance was ignored, the ICERs for the British guideline plus the NIOX devices, compared with the British guideline alone, were £6310 per QALY gained for NIOX VERO and £8250 per QALY gained for NIOX MINO.

Considerations

The Diagnostics Advisory Committee concluded that FeNO testing plus bronchodilator reversibility testing in adults and children delivered equal or greater QALYs at a lower ICER than other tests. Moreover, the Committee noted that the use of FeNO testing in conjunction with existing tests is more cost-effective than when the existing tests are used alone.

The Committee concluded that FeNO measurement should not be recommended to help with stepping down inhaled corticosteroid use in adults or children whose asthma is well managed. However, it considered FeNO measurement to be cost and clinically effective when used as an option to support symptomatic asthma management in people using inhaled corticosteroids.

Refer to Sections 5 and 6 in the original guideline document for additional information on cost analysis.

Method of Guideline Validation

External Peer Review

Description of Method of Guideline Validation

The National Institute for Health and Care Excellence (NICE) sends the Diagnostics Assessment Report (DAR), with any confidential material removed, to registered stakeholders for comment. Stakeholders have 10 working days to return comments. Models supporting the DAR are made available to registered stakeholders on request during this period.

NICE presents anonymised registered stakeholder comments on the DAR, along with any responses from NICE or the External Assessment Group (EAG), to the Committee and later publishes these comments on its website.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

The Diagnostics Advisory Committee considered clinical and cost-effectiveness evidence from a systematic review and a decision analytical model of measurement of fractional exhaled nitric oxide in asthma prepared by an External Review Group.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate use of NIOX MINO, NIOX VERO and NObreath for measuring fractional exhaled nitric oxide (FeNO) concentration in asthma

Potential Harms

False-positive and false-negative results of diagnostic tests resulting in adverse health outcomes or increased costs

Qualifying Statements

Qualifying Statements

- This guidance represents the view of the National Institute for Health and Care Excellence (NICE) and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.
- Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

Implementation of the Guideline

Description of Implementation Strategy

- The National Institute for Health and Care Excellence (NICE) has developed tools (see also the "Availability of Companion Documents" field), in association with relevant stakeholders, to help organisations put this guidance into practice. This includes

adoption support work from the NICE Health Technologies Adoption Programme.

- NICE will support this guidance with a range of activities to promote the recommendations for further research. This will include incorporating the research recommendations in section 7 of the original guideline document into the NICE guidance research recommendations database and highlighting these recommendations to public research bodies. The research proposed will also be put forward to NICE's Medical Technologies Evaluation Programme research facilitation team for consideration of the development of specific research protocols.

Implementation Tools

Chart Documentation/Checklists/Forms

Foreign Language Translations

Mobile Device Resources

Patient Resources

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

National Institute for Health and Care Excellence (NICE). Measuring fractional exhaled nitric oxide concentration in asthma: NIOX MINO, NIOX VERO and NObreath. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Apr. 52 p. (Diagnostics guidance; no. 12).

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2014 Apr

Guideline Developer(s)

National Institute for Health and Care Excellence (NICE) - National Government Agency [Non-U.S.]

Source(s) of Funding

National Institute for Health and Care Excellence (NICE)

Guideline Committee

Diagnostics Advisory Committee

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

Committee members are required to submit a declaration of interests on appointment, in every year of their tenure, and at each Committee meeting, in line with the National Institute for Health and Care Excellence's (NICE's) code of practice for declaring and dealing with conflicts of interest.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site . Also available for download as a Kindle or EPUB ebook from the NICE Web site .

Availability of Companion Documents

The following are available:

- Harnan S, Tappenden P, Essat M, Gomersall T, Minton J, Wong R, Pavord I, Everard M, Lawson R. Measurement of exhaled nitric oxide concentration in asthma; NIOX MINO and NObreath. Diagnostics assessment report. Sheffield (UK): School of Health and Related Research (ScHARR), University of Sheffield; 2013 Aug. 461 p. Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site .
- NICE diagnostic adoption support for measuring fractional exhaled nitric oxide concentration in asthma: NIOX MINO, NIOX VERO and NObreath: insights from the NHS. Electronic copies: Available from the NICE Web site .
- Communication plan template. London (UK): National Institute for Health and Care Excellence; 1 p. Electronic copies: Available from the NICE Web site .
- Diagnosis pathway from Derby Children's Hospital. Derby (UK): Derby Children's Hospital. 1 p. Electronic copies: Available from the NICE Web site .
- Clinical FENO testing algorithm. Portsmouth (UK): Queen Alexandra Hospital. 1 p. Electronic copies: Available from the NICE Web site .
- Financial resource guide to support the development of a business case: devices to measure fractional exhaled nitric oxide. London (UK): National Institute for Health and Care Excellence; 4 p. Electronic copies: Available from the NICE Web site .
- Diagnostics Assessment Programme manual. London (UK): National Institute for Health and Care Excellence; 2011 Dec. 130 p. Electronic copies: Available from the NICE Web site .

Patient Resources

The following is available:

- Measuring fractional exhaled nitric oxide concentration in asthma: information for the public. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Apr. (Diagnostics guidance; no. 12). Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site . Also available in Welsh from the NICE Web site .

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